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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/520,901

04/13/2005

Toshiyoshi Fujiwara

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EXAMINER

SHEN, WU CHENG WINSTON

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	<p><b>Application No.</b> 10/520,901</p>	<p><b>Applicant(s)</b> FUJIWARA ET AL.</p>	
	<p><b>Examiner</b> WU-CHENG Winston SHEN</p>	<p><b>Art Unit</b> 1632</p>	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 20 April 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 8-11 and 13-21.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_

13. ☐ Other: \_\_\_\_\_.

Continuation of 5. Applicant's reply has overcome the following rejection(s):

Applicant's arguments in combination with claim amendments filed on 04/20/2010 have overcome the objection of claims 13-16 and 21 under 37 CFR 1.75 as being a substantial duplicate of claims 4-7 and 12 respectively. Claims 4-7 and 12 are cancelled in the claim set filed on 04/20/2010 by Applicant.

Applicant's arguments in combination with amendments of drawings filed on 04/20/2010 have overcome the rejection claims 8-11 and 13-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The length of AdE1A and AdE1B shown in the drawings of Figure 1 filed on 04/20/2010 is consistent with the length of SEQ ID No:1 and SEQ ID No:2 disclosed in the specification and recited in claim 13 filed on 04/20/2010.

Continuation of 11. does NOT place the application in condition for allowance because:

(I) Applicant's arguments have failed to overcome the rejection of claims 8, 11, 13-17, 20, and 21 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of Li et al. (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. Cancer Res. 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC), Stuart et al. (WO 2002/20754, international publication date 03/14/2002), Nemerow et al. (WO 2000/42208, international publication date 07/20/2000), Arya (WO 2000/40741, international publication date 07/13/2000), and Hagen et al. (WO 1999/33998, international publication date 07/08/1999).

(A) Applicant argues that Stuart does Not Disclose the Nucleotide Sequence of E1A. Applicant states that to the publication of Stuart et al. (WO 2002/20754), the Office Action provides, on pages 12-13, what Applicants understand is an alignment of Stuart's SEQ ID NO:45 and SEQ ID NO: 1 of the instant application. This alignment indicates a 100.0% match between nucleotides 1-899 of Applicants' SEQ ID NO:1 and nucleotides 282-1180 of Stuart's SEQ ID NO:45. However, Stuart's SEQ ID NO:45 is just one of some 275 eDNA sequences that Stuart allegedly derived from human tissues and cell lines, and assembled into "consensus" or "template" sequences. See Stuart at lines 29-36 on page 124. In Table 2 on page 185 of that publication,

(B) Applicant argues that Nemerow does Not Disclose the Nucleotide Sequence of E1B. Applicant states that the Office Action provides an alignment of SEQ ID NO: 2 of the instant application and a GRE5-E1-SV40-Hygro" plasmid sequence from Nemerow et al. (WO 2000/42208) at pages 14-16, 2 and indicates that nucleotides 1-1823 of Applicants' SEQ ID NO: 2 are 100.0% identical to nucleotides 2123-3945 of Nemerow's GRE5-E1-SV40-Hygro plasmid. However, Nemerow does not teach or even suggest that its GRE5-E1-SV40-Hygro plasmid might contain an E1B gene, let alone identify nucleotides 2123-3945 as corresponding to such a gene. Hence, a skilled person reading Nemerow would not be able to identify in that publication any "E1 B gene consisting of the nucleotide sequence of SEQ ID NO:2" as recited in the pending independent claims of this application.

(C) Applicant argues that Arya Does Not Disclose the Nucleotide Sequence of IRES. Applicant states that an alignment of Applicants' SEQ ID NO: 3 and a "PSGT5 (SDM/RRE1/CM) backbone transfer vector" sequence from Arya (WO 2000/40741) is presented at pages 17-18 of the Office Action.<sup>3</sup> The alignment indicates that nucleotides 1-605 of Applicants' SEQ ID NO: 3 and 341- 945 of Arya's PSGT5 (SDM/RRE1/CM) backbone transfer vector are 100.0% identical. Yet Arya does not even teach or suggest that its PSGT5 (SDM/RRE1/CM) backbone transfer vector contains an IRES sequence, let alone identify nucleotides 341-945 as corresponding to such a sequence. Hence, Arya does not teach or suggest any "IRES sequence consisting of the nucleotide sequence of SEQ ID NO: 3" as called for in the pending independent claims of this application.

(D) Applicant argues that Hagen does Not Disclose the Nucleotide Sequence of hTERT. Applicant states that Finally, Applicants turn to the alignment of SEQ ID NO: 4 in this application and SEQ ID NO: 1 of Hagen et al. (WO 99/33998) shown at pages 19-20 of the Office Action. The alignment indicates at nucleotides 1-455 of Applicants' SEQ ID NO: 4 align with and are 100.0% identical to nucleotides 4669-5123 of Hagen's SEQ ID NO: 1. However, Hagen only discloses that its SEQ ID NO: 1 corresponds to "the 5'-flanking regulatory DNA sequence" of a human gene encoding a catalytic telomerase subunit. See the Hagen CA publication (Exhibit 2) at page 6, lines 5-10. Hagen does not say or indicate any specific portion that might be used as a promoter element in a genetic construct; let alone a portion that corresponding to "the hTERT promoter consisting of the nucleotide sequence of SEQ ID NO:4" recited in the pending independent claims of this application.

Applicant concludes that there is not teaching or suggestion in any of the cited references to indicate which nucleotides in those base sequences may correspond to E1A, E1B, IRES or hTERT; let alone any teaching leading a skilled person to select specific subsequences corresponding to SEQ ID NOS: 1-4 in the currently pending claims.

In response, it is noted that this maintained rejection is a 103 rejection, not a 102 rejection. In this regard, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In instant case, the names and order of genes hTERT, E1A, IRES, and E1B recited in claim 13 have been clearly taught by Mori et al. and Li et al. Stuart et al. (WO 2002/20754, international publication date 03/14/2002), Nemerow et al. (WO 2000/42208, international publication date 07/20/2000), Arya (WO 2000/40741, international publication date 07/13/2000), and Hagen et al. (WO 1999/33998, international publication date 07/08/1999) are relied on for the disclosure of the exact nucleotide sequences of SEQ ID No: 1, 2, 3, and 4 respectively. It is worth noting that genes hTERT, E1A, IRES, and E1B have been made and used in the literature for many years prior to the filing of instant application in the

context of various expression vectors as demonstrated by Stuart et al., Nemerow et al., Arya, and Hagen et al. Techniques for molecular cloning have been available to a skilled artisan for many decades after the discovery of DNA structure in 1953. Applicant is reminded that a skilled artisan will have at least a college degree in biomedical science, and most likely have a Ph.D. degree and years for postdoctoral trainings in biomedical science.

With regard to asserted requirement for specific teachings/suggestion/motivation, the Examiner would like to direct Applicant's attention, again, to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1936) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, the suggestion and motivation to combine Morin et al., Li et al., Stuart et al., Nemerow et al., Arya, and Hagen et al. have been clearly set forth on pages 8-20 of the Final office action mailed on 01/20/2010.

Finally, as documented in the Final office action mailed on 01/20/2010, the Declaration by Toshiyoshi Fujiwara filed on 11/04/2009 had been considered, and found not persuasive. The declaration clearly provides enabling support for intended use of claimed polynucleotides, thereby, consistent with the maintained 103 rejection in term of reasonable expectation of success in making and using the claimed constructs.

(II) Applicant's arguments have failed to overcome the rejection of claims 9, 10, 18, and 19 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of Li et al. (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC), Stuart et al. (WO 2002/20754, international publication date 03/14/2002), Nemerow et al. (WO 2000/42208, international publication date 07/20/2000), Arya (WO 2000/40741, international publication date 07/13/2000), and Hagen et al. (WO 1999/33998, international publication date 07/08/1999) as applied to claims 8, 11, 13-17, 20, and 21 above, and further in view of Cheng et al. (Cheng et al., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002; this reference is cited in the office action dated 06/19/2007).

Applicant's arguments and Examiner's response to Applicant's arguments are the same as documented above in the maintained rejection of claims 8, 11, 13-17, 20, and 21 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. in view of Li et al., Stuart et al., Nemerow et al. (WO 2000/42208, international publication date 07/20/2000), Arya (WO 2000/40741, international publication date 07/13/2000), and Hagen et al.

(III) Applicant's arguments have failed to overcome the rejection of claims 8-11 and 13-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Morin et al. (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of Yu et al. (US 6,692,736, issued on 02/17/2004, filed on 03/21/2001) Stuart et al. (WO 2002/20754, international publication date 03/14/2002), Nemerow et al. (WO 2000/42208, international publication date 07/20/2000), Arya (WO 2000/40741, international publication date 07/13/2000), and Hagen et al. (WO 1999/33998, international publication date 07/08/1999).

Applicant's arguments and Examiner's response to Applicant's arguments are the same as documented above in the maintained rejection of claims 8, 11, 13-17, 20, and 21 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. in view of Li et al., Stuart et al., Nemerow et al. (WO 2000/42208, international publication date 07/20/2000), Arya (WO 2000/40741, international publication date 07/13/2000), and Hagen et al.

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